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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,233	12/01/2003	Arne Holm	P63882US1	3256

136 7590 07/02/2007

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
07/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/724,233	HOLM ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84-95* is/are pending in the application.

4a) Of the above claim(s) *94 and 95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 84-95 are pending

Claims 94 and 95 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species.

Claims 84-93 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 84-93 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons reiterated below. [This is a new matter rejection].

Claim 84 drawn to Formula (I) with the corresponding definitions of each of the variables in said formula; Formula II-Formula VI are not supported in the original disclosure.

Likewise the claim to a "plurality of identical, fully side-chain protected peptide sequences" and "between 4 and 20 naturally occurring L-amino acid residues" are not supported in the as-filed specification. The as-filed specification does not recite for any compounds of the recited formulae. Cf. original claim 1. MPEP 714.02 clearly states that applicants point out where in the specification support can be found.

Response to Arguments

Applicants have included Attachment A in the instant response that schematically explains the Applicants' invention and the derivation of the Formulas in claim 84 and further described below. Support for the description of the general process is found at page 13, line 28 to page 18, line 12 of the specification. In page 1/5 of Attachment A, Figure 1 depicts the OspC antigenic determinant peptide. A critical characteristic of the OspC antigen is that it must be presented in a C-terminal orientation to bind to antibodies, which is not how standard peptides are presented for antibody binding. In Figure 2, a lysine tree is shown from the J.P. Tam reference. The Tam reference teaches a method of generating many N-terminal presenting peptides. Figure 3 shows the same Tam prior art method of multiple antigen presentation, known as the MAP system, using the OspC sequences. The MAP system is limited to

N-terminal presentation of peptides, therefore it cannot be used to bind antibodies specific for C- terminal ends of the antigenic peptide. On page 2/5 of Attachment A, Figure 4 illustrates the problem being solved by Applicants' invention, namely presentation of peptide antigens in a C-terminal orientation, instead of an N- terminal orientation. Figure 5 shows what the desired multiple antigen presentation would look like. There, two OspC peptides are linked at their N-terminals and have free C-terminal ends able to bind to immune response receptors. Page 3/5 of Attachment A is a schematic illustration of the method of Applicants' invention. Figure 6, top, depict a resin bead in a solid-state synthesis of a desired antigen peptide after completion of the synthesis of the peptide (See, the specification at page 18, line 30 - Page 21, line 20; page 41, line 5 - page 47, line 27). It is during this step, that measurement of the amount of substitution of peptides (mole/g resin) is performed to identify how many moles of dicarboxylic acid must be added to obtain a 1:1 mixture of acylated and un-acylated peptide chains. Two standard methods for measuring the substitution are provided in the specification, in the Examples section entitled, "Estimation of the coupling yield of the first N-a-amino protected amino acid"(page 45, lines 13-23). Figure 6 shows that the synthesized peptides are attached to the resin

bead at the C-terminal end, and the N-terminal ends of the peptides are free. In Figure 6, at the bottom, the peptide chains are shown as acylated with 0.5 equivalents of an achiral dicarboxylic acid represented by XN(CH2COOH)2, so that approximately half of the free a-amino groups of the fully side-chain protected peptide chains, react with the achiral dicarboxylic acid. Again, the dicarboxylic acid groups should be achiral because this is the only way to prevent racemic mixtures of peptides. On page 4/5 of Attachment A, Figure 7 illustrates acylation of the remaining free N-terminal ends in step 2 of the process of the claimed invention, with the free carboxylic acid group now present on the other half of the bound peptide chains. The dicarboxylic acids are activated, and the reaction of the free COOH group with a free N-terminal of the remaining peptides results in a cyclization of two peptides with a dicarboxylic acid group as shown in Figure 7, bottom. (Page 20, lines 20-33; Page 21, line 21 - Page 22, line 30) On page 5/5 of Attachment A, Figure 8 shows the next step in the claimed process. Here the cyclized di-peptides from Figure 7 are cleaved from the resin bead using the standard Fmoc deprotection and cleavage methods used in solid phase peptide synthesis. The result is the LPA molecule claimed having two peptides linked at their N-terminal ends by an amino group, and having their C-terminal ends free

(Page 23, lines 1-30). Applicants have supplied the foregoing support for the amended claims as requested by the Examiner.

In response, claim 84, for example, does not recite the species OspC peptides, rather only peptide of the given formula. However, a support for a species is not a support for the general formula, as claimed. Applicant's reliance and comparison with the Tam reference is unclear when Tam is not cited as prior art. Furthermore, it is not clear how Formula III with b define as 0.4(a) can be a fraction i.e., how can the amino acid sequence be given in terms of a fraction? The specification at e.g., page 14, line 14 positively recites the dicarbocylic acid of the general formula as-filed. It does not recite the instant amended formula with the variables a and b (m and n, as filed) and not in fraction. (It is suggested that applicants recite the formula as given in the as-filed specification e.g., page 14 and page 16, line 19).

Written Description Rejection

Claims 84-89 and 91-93 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention for reasons as repeated below.

To satisfy a written description requirement for a claimed genus a sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. A representative number of species means that the species, which are adequately described, are representative of the entire genus.

The specification does not describe a method of solid phase synthesis for preparing a ligand presenting assembly (LPA) having undefined amino acids sequences between 4 and 20 amino acids. Furthermore, the specification does not disclose that any achiral dicarboxylic acid with 0.4-0.6 equivalents can be employed in the synthesis of a peptide with no primary sequence and that such amount would result in a peptide with no racemization effect. It is well known in the art that solid phase synthesis would require the amino acid sequences for the

synthesis to occur. Given no amino acid structures, it is not clear as to the kind of amino acids or combinations thereof that can be synthesized by solid phase. It is well known in the art that synthesis of longer amino acid sequences may result in ring formation or require activation condition, which could prevent formation of well-defined products with optically active bridging compounds. In biotechnological invention one cannot necessarily claim a genus after only describing a single species because there may be unpredictability in the results obtained from species other than those specifically described. The specification does not describe the correlation between the species recited therein to the huge scope of the genus having no primary sequences for the claimed peptide sequences.

Response to Arguments

Applicants submit that the claims as presented are substantially limited to the use of simple achiral dicarboxylic acids as the bridging group. The general applicability of these acids is illustrated with imino diacetic acid (Examples 1, 2 and 6), 3-amino glutaric acid (Examples 3, 4 and 5), glutaric acid (Examples 7, 9. i0 and ii) and tricarballylic acid (Example 8). Please note that although tricarballylic acid is in fact a tricarboxylic acid, it is used as a dicarboxylic acid, see e.g.

Example 8, wherein the surplus carboxy group is available for subsequent coupling.

In response, the applicability of the acids to a single defined peptide sequence wherein the amino acid residues are given in the sequence e.g., OspC peptide is not controverted. What is at issue is the general applicability of said acids to a genus of no defined peptide sequence. Applicants submit that it was routine at the time of filing the original application (September 29, 1998), to make peptides using solid phase synthesis techniques of 4-20 amino acids in length, regardless of the sequence. Applicants state that even longer peptides, of 40 or more amino acids, were well within the scope of those of ordinary skill at the time of filing. Applicant invites the Examiner to review copies of abstracts of published scientific literature found in PubMed, which are directed to creation of various peptides using solid phase synthesis and attached collectively hereto as Attachment B. In Attachment B, Applicants provide abstracts of prior art papers dating back to 1984, showing that synthetic peptides having more than 20 amino acids were well within the scope of those skilled in the art. Examples of synthesized peptides include human growth hormone (hGH, 29 amino acids), vasoactive intestinal peptide (VIP, 31 amino acids), follicle stimulating hormone (FSH, 48 amino acids), and

chaperonin i0 (I01 amino acids). These references clearly show that 4-20 amino acid peptides are not problematic and, in fact, were routinely prepared in peptide synthesis machines, at the time Applicants' application was filed. Furthermore, the state of the art has progressed to where peptide synthesizers easily make i00 amino acid peptides of any sequence. See, for example, the sales brochure of Applied Biosystems, Inc.'s (Foster City, CA) peptide synthesizing machine, the 433A, which is attached hereto as Attachment C. Applicants submit that the general applicability of the method of the invention for preparing LPA for presentation of peptide sequences has been illustrated for a wide number of sequences from different sources, for example, Borrelia burgdorferi (Examples 1-5), Mycobacterium tuberculosis (Examples 5- 6), Chlamydia trachomatis (Examples 7-8 and Chlostridium thermosacchrolyticum (Example 12), as well as sequences derived from angiotensin-I (Examples 9-12).

In reply, as shown in the all of the references all the peptide sequence are of defined amino acid sequence and not without a sequence, as claimed. None of the above cited references have been shown to have use achiral dicarboxylic acid in the peptide sequence in order to prevent racemization. Since applicants submit they are the first one to discover that the use of dicarboxylic acid in any peptide sequence prevents

racemization hence, applicants have to show by a reasonably number of species that the dicarboxylic acid is applicable to a genus as claimed.

(Limiting the claims to the peptide obtained from Borrelia burgdorferi, Chlamydia trachomatis, Chlostridium thermosacchrolyticum and angiotensin-I would overcome this rejection).

Claim Rejections - 35 USC § 112

Claims 87, 89 and 91-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons as restated below.

1. Claim 87 is unclear as to the term "derived". It is unclear as to how the peptide sequences are derived from OSPC protein of Borrelia. It is a native fragment or a peptide with modification therein? This claim has similar import to claim 89.

Response to Arguments

Applicant states that one of ordinary skill in the art would understand what Applicant means by the term "derived" in claims 87 and 89. The meaning of the term is clearly spelled out

in the specification from page 26, line 30 to page 31, line 24. The phrase "derived from Borrelia Osp C protein" means that there is a sequence homology between the claimed peptide sequence and the Osp C protein sequence. The sequence could be a fragment, or a portion of the OsP C protein, which is sufficient to elicit an immune reaction.

In reply, the claims do not recite a function of the peptide e.g., to elicit immune response such that the peptide derived is readily apparent. Furthermore, it not clear as to the homology of e.g., a fragment from the parent given no direction as to which specific amino acid in a peptide sequence is homologous to the numerous residues in the parent peptide. (It is suggested that "obtained" from the specific parent protein e.g., Borrelia protein be used to obviate this rejection).

2. The representation of e.g., Formula III with "> S" is unclear and confusing as to how it is connected to the other moieties.

Response to Arguments

Applicant submits that formula III is depicted in Applicant's Response of November 20, 2006 in Attachment A at Figures 6 and 7. Formula III is a schematic representation of the styrene bead (S) where one of the two polypeptide chains has been activated with a dicarboxylic acid moiety (R) [HOOC-R-CO-

HN-A-CO] b), and the other adjacent polypeptide chain has not been activated [H2N-A-CO]a-b, because of the addition of about half of an equivalent of dicarboxylic acid for each peptide chain. This is clearly depicted as the second diagram in Figure 6, and the first diagram in Figure 7 of Attachment A of the November 20, 2006 Response.

In response, as stated above this formula is not supported in the as-filed specification. Hence, applicant's diagrammatical representation of the formula is not clear(this formula was submitted as an amendment not originally present in the as-filed specification).

Withdrawn Rejections

In view of applicant's arguments the 35 USC 102 rejections over Bhatnagar, Lange and Albert are withdrawn.

Claim Rejections - 35 USC § 103

Claims 84-89 and 91-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Bhatnagar et al (J. Med. Chem.) or Lange in view Mathiesen (WO 97/422210) for reasons given below.

Bhatnagar et al disclose at page 3814, Fig. 1 a method of solid phase synthesis of a dimer as shown at Fig. 1. The

complete synthesis is described under Chemistry section, page 3814 up to page 3815. The synthesis uses 0.5 mol equivalents of the diamino dicarboxylic acid.

Lange discloses a method of solid phase of dimeric peptide Bradykinin containing a diaminodicarboxylic acid linker. See e.g., the abstract at page 289 and the detailed solid phase synthesis at e.g., page 90, Materials and Methods. The method of Lange using specific Bradykinin peptides with dicarboxylic linker fully meets the claimed method of solid phase of a ligand assembly, as broadly claim.

Each of Bhatnagar et al or Lange references does not disclose applying the solid phase synthesis to a peptide derived from OspC of Borelia burgforferi. However, Mathiesen discloses a method of making a peptide from a sequence of OspC of Borelia burgforferi having the sequence of Seq. ID. 1 and the variants thereof by solid phase synthesis. See e.g., the abstract; page 6, line 20 and pages 34-35 as to the solid phase synthesis of the sequence referring to the method of Holm (1989) and Meldal. Mathiesen discloses that the use of this short peptide which form a part of the antigenic epitope is essential in the human immunological recognition of OspC (page 4, lines 25-31), which has a number of advantages. For example, it simplifies the preparation and purification steps of the components of the

assay and helps standardize the assay. See e.g., page 5, lines 3-35). Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to synthesize in the method of either Bhatnagar or Lange the peptide from OspC of Borelia burgforferi for the advantages taught by Matheisen in the used of said short peptide sequences. One would be motivated to synthesize a dimer for greater immunological responses to said OspC of Borelia burgforferi antigen.

Response to Arguments

Applicants respectfully submit that Bhatnagar et al. and/or Lange et al. fail to teach a method of solid phase synthesis of a ligand presenting assembly (LPA) where the peptides are synthesized such that they create a dipeptide being connected by an achiral carboxylic acid at their N-terminus, and have free C-terminal ends. The methods of synthesis and the resulting products of both Bhatnagar et al. and Lange et al. are completely distinct from Applicants' claimed method. This failure is not cured by the addition of the teachings of the Borrelia sequences in the Mathiesen et al. reference. The combination of Bhatnagar et al. or Lange et al., in view of Mathiesen et al., does not teach each and every element of Applicants' claimed invention.

In reply, as applicant admitted above, solid phase synthesis is now routine and in fact is now automated hence, it would be within the ordinary skill in the art to synthesize either at the N or C-terminus, given a peptide sequence. Each of Bhatnagar and Lange discloses a specific peptide sequence and uses a charged residues i.e., diaminodicarboxylic acid as opposed to the instant claimed charged residue dicarboxylic imino acid, it would be within the ordinary skill in the art at the time the invention was made to use either one charged residue over the other. It is well known in the art that these charged residues, i.e., diaminodicarboxylic acid or imino diacetic acid have been substituted one over the other. In the absence of new and unexpected results especially in applying the instant imino diacetic acid to a known peptide, the claimed method of solid phase synthesis is prima facie obvious to one having ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claim 90 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 1st paragraph, set forth in

this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

This application contains claims 94-95 drawn to a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0765. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
June 21, 2007